REMARKS/ARGUMENTS

Claims 1, 3-5, 8, 10, 46, and 47 have been revised to utilize the phrase "consisting of" in place of "comprising" at the start of the claims. Claims 1, 4, 8, and 46 have also been revised to state that the peptides bind $\alpha 3\beta 1$ integrin (with claim 4 having been re-written in independent form), which is supported by the instant application at least on page 11, lines 27-30, and to revise extraneous recitations of "peptide". Claim 1 has also been revised for correction of clerical informalities in language. These revisions are not made in acquiescence of any rejection of record but rather is made to better tailor the claims to currently contemplated clinical embodiments of the invention. Accordingly, the revision is made for reasons related to commercial and business considerations rather than any issue of patentability.

Claims 1 and 5 have also been revised to delete reference to serine at position X_1 and SEQ ID NO:52 based on the telephonic discussion of December 20, 2004 in which Examiner Haddad explained the scope of the search that had been conducted.

Claim 46 has also been revised to introduce the appropriate Sequence Identifier without altering the scope of the claim.

Claims 2 and 9 have been revised to recite the intended scope wherein the tetrameric sequence is present in the peptides of the claims. The scope of claims 2 and 9 have not been changed because they necessarily had all the limitations of claims 1 and 8, from which claims 2 and 9 depend, respectively. Additionally, the claims have been revised to refer to "up to 12 amino acids in length" based upon the revisions to claims 1 and 8, which are directed to peptides from 5 to 13 amino acids in length. Support is provided in claims 2 and 9 as originally presented.

Claim 7 has been revised to be consistent with revised claim 1.

Claims 11, 12, 15-19, and 31-45 have been canceled as being directed to non-elected inventions. Applicants reserve the right to re-present them in a divisional or other continuing application without prejudice.

Claims 13 and 14 have been revised based upon helpful suggestions from Examiner Haddad on December 20, 2004.

Claims 20-26, and 28-30 remain pending because they are subject to rejoinder as discussed below. Claims 20, 26, 29, and 30 have been revised to be directed to "*in vitro*" methods without any acquiescence to any rejection of record. Instead, the changes are made to better tailor the claims to currently contemplated embodiments of the invention. Accordingly, the revision is made for reasons related to commercial and business considerations rather than any issue of patentability.

New claims 48-52, all dependent from claim 46, have been introduced. These claims correspond to claims 2, 3, 7, 13, and 14 and reflect claimed subject matter when the content of claim 46 was previously present in claim 1. Applicants respectfully submit that these new claims require no additional consideration and ask that they be considered and allowed along with claim 46.

No new matter has been introduced, and entry of the amendments is respectfully requested.

Telephonic Interviews of November 17, 2004 and December 20, 2004

Applicants express their thanks for the courtesy of a telephonic interview between Examiners M. Haddad and C. Chan as well as M. Bahar of the NIH (party at interest) and the undersigned on November 17, 2004. Applicants wish to express their appreciation for the indication that the "new matter" rejection will be withdrawn.

The interview included discussion of all examined claims and cited references from the last Office Action. Applicants' representatives indicated their willingness to consider revising claims to utilize "consisting of" as the transitional phrase and to state that the peptides bind $\alpha 3\beta 1$ integrin. The Examiners indicated that such amendments would likely obviate both the rejections based upon cited references as well as rejections under 35 U.S.C. § 112.

Applicants also express their appreciation for the courtesy of a telephonic discussion between Examiner Haddad and the undersigned on December 20, 2004. In addition to pointing out the scope of the sequence search and examination conducted, Examiner Haddad offered helpful suggestions to the language of the previously submitted response (filed November 24, 2004). The undersigned indicated that Applicants would consider the suggestions before responding. It was agreed that the November 24, 2004 response would not be entered in favor of a new response by Applicants that would incorporate Examiner suggested revisions as acceptable to Applicants to place the application in condition for allowance. Applicants respectfully submit that this has been accomplished with the above revised claims.

Rejoinder

Claims 20-30 and 37-45 remain directed to methods comprising the use of a peptide according to claim 1 (claims 20-29 and 37-45) or claim 2 (claim 30). As such, they have all the limitations of elected claims 1 and 2 and are subject to rejoinder as set forth at MPEP 821.04. Applicants respectfully ask that claims 20-30 and 37-45 be rejoined and allowed along with claims 1 and 2.

Based upon the December 20, 2004 telephonic discussion, however, Applicants have chosen to pursue claims 37-45 without prejudice for pursuit in a continuing application rather than in the instant application. Accordingly, rejoinder of claims 20-26 and 28-30, because claim 27 has been canceled as superfluous in light of the revisions to claims 20, 26, 29, and 30, is respectfully requested.

Claim Objections

Claim 46 was objected to under 37 CFR 1.821(d) because it lacks a sequence identifier. Applicants respectfully request withdrawal of this objection in light of the amendment to claim 46.

Claim Rejection under 35 U.S.C. § 112, second paragraph

Claims 2 and 9 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for reciting "from about 4 to about 12 amino acids" because "[i]t is unclear how many amino acids constitute 'about'".

Applicants respectfully, but strongly, traverse the instant rejection as failing to present a *prima facie* case of indefiniteness for the reasons provided in the last response. Specifically, it is well settled law that the term "about" is not indefinite *per se*. This standard was not applied in the instant situation, which is appears to be based upon the view that "about 12" is indefinite in the absence of a definition (and thus *per se* indefinite).

However, and in light of the revisions to claims 1 and 8 to use "consisting of" as the transitional phrase, "about 12" is delimited by the maximum length of 13 as provided for by the literal scope of the claims. Accordingly, the claims have been revised to recite "up to 12 amino acids" in the interest of advancing prosecution of the instant application. Applicants thus respectfully submit that the instant rejection has been obviated and so withdrawal is requested.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7-10, 13, 14, 46, and 47 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to "reasonably provide enablement for any peptide 'comprising'" the sequences recited in claims 1, 8 and 46.

As an initial matter, Applicants respectfully submit that no issue of non-enablement exists in light of the claim revisions provided above, which exclude the use of "comprising" and include the statement that the peptides bind $\alpha 3\beta 1$ integrin. Accordingly, Applicants believe that no *prima facie* case of undue experimentation exists, especially in light of the standard set out in part at MPEP 2164.04, including *In re Marzocchi*[1] and the other cases cited therein.

[1] 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

Once again, Applicants point out that no objective reason has been provided to question that undue experimentation is needed to make and use the claimed peptides, which are now of defined lengths, as encompassed by the revised claims.

To the contrary, the instant invention is similar to the situation seen with a common integrin binding motif, Arg-Gly-Asp (RGD) as discovered via fibronectin. In the case of the RGD sequence, there is no reason to doubt that it is possible to make and use a variety of peptides containing the sequence, which retain the ability to bind integrin, without undue experimentation. This follows because while there may be some unpredictability as to whether some peptides having the RGD sequence will misfold as to present a structure that will not bind integrin, the amount of experimentation necessary to address this unpredictability is not undue.

The instant invention is directed to an analogous situation because no objective reasons have been provided as to why the instant tetrameric sequence, as recited in claims 1, 8, and 46, cannot be treated in the same manner as the RGD sequence known in the art. Both sequences are in the same, and more specific, field of integrin binding peptides. Accordingly, the reliance upon the articles by Kuntz et al. and Miller et al. (in the previous Office Action mailed May 21, 2004) is misplaced because the content of both fail to take either the RGD sequence or the instant tetrameric sequence into consideration. Instead, the content of both paint a picture of the situations with other proteins and polypeptides that are unrelated to the peptides of the invention. Accordingly, Applicants respectfully submit that the contents of those references are not dispositive relative to the instant application.

A much more relevant comparison to the instant application is present in *In re Wands*[2] (copy attached), where no undue experimentation was present to support an assertion of a lack of enablement. The facts of *Wands* involve claims directed to immunoassays to detect hepatitis B surface antigen (HBsAg) by use of monoclonal antibodies (MAb)which bind the antigen, wherein the MAb have a high affinity of at least 10^{-9} M for the antigen. The claims were solely rejected as requiring undue experimentation to make the MAb needed to practice the

[2] 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

invention. The Patent and Trademark Office (PTO) took the position that "data presented by Wands show that the production of high affinity IgM anti-HBsAg antibodies is unpredictable and unreliable."[3] There was no issue of "how to use" the *Wands* invention because, like in the instant application where one skilled in the art would know how to use the peptides to bind $\alpha 3\beta 1$ integrin as disclosed, one skilled in the art would know how to use the high affinity MAb in the claimed immunoassays.

The Federal Circuit accepted the Wands argument that "methods to make high-affinity IgM anti-HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation."[4] More specifically, the Federal Circuit stated clearly that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening."[5] The court then continued by reviewing the process for producing monoclonal antibodies by use of hybridoma cells followed by the following:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which one secrete antibodies with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.... Furthermore, in the monoclonal antibody art it appears that an 'experiment' is not simply the screening of a single hybridoma but is rather the entire attempt to make a monoclonal antibody against a particular antigen.... Wands carried out this entire procedure [to make a monoclonal antibody] three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations.[6]

The Federal Circuit then proceeded to conclude that no undue experimentation was needed to obtain antibodies to practice the claimed invention.

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[3] *Id.* at 1402.

[4] *Id.* at 1404.

[5] *Id.*

[6] *Id.* at 1406-7.

The facts and law in *Wands* are directly applicable to the instant invention because like MAb, the claimed peptides are polypeptides that bind a target molecule (HBsAg in *Wands* and $\alpha 3\beta 1$ integrin in the instant invention). The situations are also similar in the sense that like the MAb situation, the claimed peptides are not prepared by an "experiment" that is simply the screening of a single peptide. To the contrary, the instant peptides can be prepared in combinations such that multiple peptides are prepared and screened simultaneously where the skilled artisan is prepared to screen "negative" peptides that do not have $\alpha 3\beta 1$ integrin binding activity.

This latter parallel between *Wands* and the instant application is demonstrated not only by the peptides shown on page 34, Table 2, of the application, but also by the results of alanine scanning across the binding sequence as shown on page 36, Table 3. Table 3 shows that substitution of an alanine (alanine scanning mutagenesis) for 9 of 12 positions[7] in a dodecameric peptide containing the NVRF tetrameric sequence, the binding affinity is unchanged for positions outside the tetrameric NVFR core motif. Accordingly, one skilled in the art presented with these results would expect that the majority, if not all, of positions outside the tetrameric core motif may be substituted with other amino acid residues without deleterious effects on binding to $\alpha 3\beta 1$ integrin. *The instant statement of the rejection provides no objective reason to counter this view.* Moreover, and because the facts of *Wands* are so much more applicable to the instant application, no reliance on *In re Fisher* is acceptable where it is differs from the situation in Wands and the instant invention.

Therefore, and to the extent that any residual concern may be present with respect to enablement for the revised claims based upon a possible need for screening assays or the definitions of the R_1 and R_2 groups in the claims, Applicants respectfully submit that as previously explained, no more than routine and repetitive experimentation, like that in *Wands*, is needed to make and use the instantly claimed invention.

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[7] The three unsubstituted positions are those occupied by Gly (third residue), Val (fourth residue), and Val (eleventh residue), which are already small side chain residues like alanine.

This position is also applicable to claims 13 and 14 (as well as new claims 51-52) because contrary to the statement of the rejection, the instant application describes the use of peptides to inhibit vascularization in a chick chorioallantoic membrane, or CAM, (see pages 47-48, Table 5) as well as modulate endothelial cell and SCLC proliferation and other behavior (see pages 40-46). The correlation between a CAM assay and angiogenesis is well known such that the former is used as a screen to increase the expectation of successfully using a molecule to inhibit the latter. The ability to inhibit cell activities *in vitro* provides a reasonable basis to support the claims as filed.

Given the guidance provided by the instant application and the absence of objective reasons to doubt the presence of an enabling disclosure given the disclosure as provided, the claimed invention must be **presumed enabled**. Accordingly, Applicants respectfully request withdrawal of the instant rejection.

Claims 1-5, 7-10, 13, 14, 46 and 47 were rejected under 35 U.S.C. § 112, first paragraph as allegedly "failing to comply with the written description requirement." Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of an inadequate written description has been presented.

As an initial matter, Applicants point out that the statement of the rejection asserts that

> there is no described or art-recognized correlation or relationship between the structure of the invention, the generic formulae and it's anti-angiogenic, anti-proliferation function (i.e., inhibition of a $\alpha 3\beta 1$/TSP interaction), the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of variants which retain the features essential to the instant rejection. (see page 6 of the previous Office Action)

Applicants respectfully submit that contrary to the position reflected by the above quote, the instant application clearly asserts that the disclosed tetrameric core motif is

responsible for (or correlated with) the activities of the invention as disclosed. Moreover, Applicants strongly disagree with the apparent assertion that the correlation needs to be "art-recognized". How can this be the standard? Is it not possible for an application, like the instant one, to disclose a correlation between structure and function for the first time? Applicants respectfully submit that this possibility must be available and so the view taken in the instant rejection cannot stand.

Additionally, the above quote seems to admit that the instant application discloses at least anti-angiogenic and anti-proliferative uses of the claimed invention in relationship to $\alpha 3\beta 1$ integrin binding. This is at odds with the rejection addressed above, which asserted that no such properties were available for the use of the compositions of claims 13 and 14 (as well as claims 51 and 52).

To the extent that this rejection is based upon the view that amino acid residues in the R_1 and R_2 groups must be defined to provide a written description, Applicants strongly disagree because the invention is based upon the tetrameric core motif as claimed. This is supported by the data on page 36, Table 3. Applicants believe that it is improper for the Office to redefine the invention to be something other than that which Applicants claim.

In light of the above, as well as the **strong presumption** of an adequate written description as discussed in the previous response, Applicants simply do not believe that any issue of an inadequate written description is present. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 46 was also rejected under 35 U.S.C. § 112, first paragraph as allegedly containing "new matter." As noted above, Applicants understand that this rejection has been obviated based upon the discussion during the telephonic interview of November 17, 2004, where support for claim 46 as found in original claim 1 was sufficient.

Applicants respectfully request an indication of this rejection has having been withdrawn.

Claim Rejections under 35 U.S.C. § 102

Claims 1-2, 5, and 13-14 were rejected under 35 U.S.C. § 102(a) as allegedly anticipated by JP10-25896 (9/1998). This was discussed during the telephonic interview where the actual teachings of the cited reference were unclear in the absence of a translation of the relative portions of the document. For example, it is unclear whether the sequence in the reference as relied upon is merely a portion of a larger sequence.

While Examiner Haddad will endeavor to obtain a translation of the cited reference, Applicants point out that this rejection is not applicable to the revised claims, which no longer recite "comprising". Accordingly, this rejection may be properly withdrawn.

Claims 1-2 and 5 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Fowlkes et al. (USP 5,789,184).

Applicants have carefully reviewed the statement of the instant rejection and respectfully point out that the reference fails to actual disclose a peptide. Fowlkes et al. only describe the isolation of plasmids containing particular sequences that are manually interpreted as encoding the sequence of SEQ ID NO:55 in the reference (see column 61, lines 40-59). This is not a disclosure of an actual peptide having that sequence because no such peptide is taught to exist. Applicants respectfully submit that it is entirely possible that the peptide is not expressed or is expressed as a larger or truncated version. Simply put, it is not clear whether a peptide having only SEQ ID NO:55 is actually in existence based on the cited reference. Accordingly, no *prima facie* case of anticipation has been presented.

Moreover, Applicants point out that this rejection is not applicable to the revised claims, which no longer recite "comprising". This presents a second reason why no *prima facie* case is present. Accordingly, this rejection may be properly withdrawn for both of these reasons.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 7-9 and 13-14 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over either of JP10-25896 or Fowlkes et al. in view of USP 5,770,563 (Roberts et al.).

Applicants have carefully reviewed the statement of the instant rejection and respectfully submit that no *prima facie* case of obviousness has been presented. As noted above, neither of JP10-25896 and Fowlkes et al. is properly applicable to the claims from which claims 7-9 and 13-14 depend. Accordingly, this rejection may be withdrawn for this reason.

Additionally, Applicants respectfully point out that no adequate reason or motivation has been provided for why an ordinary artisan would combine the references as alleged. The teachings of JP10-25896 are unclear for the reasons provided above. Given no knowledge as to that disclosure, why would one of ordinary skill combine it with the thrombospondin peptides of Roberts et al.? The simple answer is that they would not in the absence of impermissible hindsight reconstruction.

Similarly, why would the ordinary artisan combine the teachings of Fowlkes et al., which relate to yeast pheromone technology, combine them with the thrombospondin peptides of Roberts et al.? Again, there would be no suggestion or motivation without use of impermissible hindsight based on the instant application.

In addition to these reasons, Applicants point out that this rejection is not applicable to the revised claims, which no longer recite "comprising". Accordingly, this rejection may be properly withdrawn for all of these reasons.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and urge an action to that end followed by passage of the Application to issuance.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6151.

Respectfully submitted,

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